

## Sprimeo

Procedural steps taken and scientific information after the authorisation

| No       | Scope  | Opinion/<br>Notification <sup>1</sup><br>issued on | Commission<br>Decision<br>Issued <sup>2</sup> /<br>amended on | Product<br>Information<br>affected <sup>3</sup> | Summary  |
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| WS/0189  | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data   | 19/04/2012   | 25/05/2012  | SPC   |  |
| A20/0067 | Article 20 Review<br><br>On 20 December 2010, the European Commission initiated a procedure under Article 20 of Regulation (EC) No 726/2004 for all aliskiren-containing medicinal products authorised in the centralised procedure and requested the CHMP to assess all the available data and its impact on the risk benefit balance for aliskiren-containing medicinal products and to give its | 16/02/2012   | 20/04/2012  | SPC, Annex II, PL                               | Please refer to the Assessment Report: Sprimeo-H-851-A20-67-Assessment Report-Article 20 |

<sup>1</sup> Notifications are issued for type I variations (unless part of a group or a worksharing application). Opinions are issued for all other procedures.

<sup>2</sup> No Commission Decision is issued for type IA and type IB variations or for type II variations and annual re-assessments that do not affect the annexes.

<sup>3</sup> SPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

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|           | <p>opinion on whether the marketing authorisations for these products should be maintained, varied, suspended or revoked.</p> <p>The scope of the review was to assess the risk benefit balance of all aliskiren-containing medicinal products in the approved indication of hypertension in light of the emerging safety data from the ALTITUDE study in patients with diabetes at high risk for cardiovascular and renal events which lead to the premature study termination.</p>                                       |  |   |   |         |
| IG/0148/G | <p>This was an application for a group of variations.</p> <p>C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD,</p> <p>C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system</p> | 22/02/2012   | n/a   |   |         |
| WS/0191/G | <p>This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p>   | 16/02/2012   | 16/02/2012  |   |         |

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|         | <p>The specification of the active substance aliskiren has been tightened. The test procedures used for aliskiren have been updated.</p> <p>In addition, typographic errors have been corrected in the dossier.</p> <p>All those changes apply to both routes of synthesis of aliskiren (Synthesis B and synthesis C), where applicable.</p> <p>B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent</p> <p>- Tightening of specification limits,</p> <p>B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure,</p> <p>B.I.b.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised,</p> <p>B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate</p> |  |   |   |  |
| WS/0145 | This was an application for a variation following a worksharing procedure  | 20/10/2011   | 22/11/2011  | SPC, PL   | Toxic epidermal necrolysis (TEN) is considered severe cutaneous adverse reaction (SCAR) as it is severe, |

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|         | <p>according to Article 20 of Commission Regulation (EC) No 1234/2008. Update to section 4.8 of the SmPC to include severe cutaneous adverse reactions including toxic epidermic necrolysis and oral mucosal reactions, following the assessment of PSUR 5. The MAH has submitted consequential changes to the Package Leaflet. In addition, minor changes have been made in the Section 2 of the Package Leaflet with regards to angioedema for Rasilez, Rasilez HCT, Riprazo and Sprimeo.</p> <p>C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH</p> |  |   |   | <p>unpredictable, and drug-induced. TEN is characterized by extensive detachment of the epidermis and erosions of the mucous membranes. In response to request from CHMP, the MAH has conducted comprehensive review in which cases of SCARs have been identified where the causal relationship with aliskiren cannot be ruled out in the absence of alternative explanations. Considering the severity of the described reactions, the CHMP requested "SCARs" including "TEN" and "oral mucosal reactions" to be added in section 4.8 of aliskiren containing product SmPC.</p>  |
| WS/0146 | <p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a</p>   | 20/10/2011   | 22/11/2011  | SPC, PL   | <p>Arthralgia is a nonspecific symptom which can be associated with various medical conditions. The most frequent are osteoarthritis, gout, bursitis, infectious diseases, injury, osteomyelitis, and autoimmune diseases. However, it is also considered that hypersensitivity/allergic reactions sometimes manifest with systemic involvement including arthralgia. Joint swelling is also very commonly associated with the above mentioned joint disorders, or could be linked to peripheral oedema or to systemic manifestation of hypersensitivity reactions.</p> <p>This review focused on arthralgia and joint swelling cases where underlying hypersensitivity reactions likely played</p> |

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|         | <p>Core SPC - Change(s) with new additional data submitted by the MAH</p> <p>C.1.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH</p>  |  |   |   | <p>a role in the development of arthralgia and where both conditions could have been due to the direct effect of aliskiren.</p> <p>In response to the request from CHMP, MAH conducted a comprehensive review of all cases of "Arthralgia". Based on this new analysis, CHMP requested the addition of the ADR "Arthralgia" in section 4.8 of aliskiren containing product SmPCs.</p>   |
| WS/0169 | <p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.3 of the Summary Product Characteristics (SmPC) to remove verapamil from the contraindications, and sections 4.4 and 4.5 of the SmPC, following the CHMP assessment of the data regarding the potential for interaction of aliskiren with verapamil, and the impact of Pgp inhibition on the distribution of aliskiren. The Package Leaflet has been updated accordingly. In addition, MAH took opportunity to update the contact details of local representatives in the PIL for Riprazo, Sprimeo and Riprazo HCT. This application is submitted in fulfilment of the FUM001 for Riprazo HCT and Sprimeo HCT</p> <p>C.1.4 - Variations related to significant modifications of the SPC due in</p> | 22/09/2011   | 27/10/2011  | SPC, PL   | <p>Contraindication with regards to concomitant use of aliskiren and the highly potent P-gp inhibitor ciclosporin and other potent P-gp inhibitors (verapamil, quinidine) was introduced on the basis of results from drug-drug interaction study. Subsequently, as a part of Rasilez FUM 015 MAH was requested to provide additional preclinical data evaluating the potential mechanism of the ciclosporin and other potent P-gp inhibitor interaction with aliskiren. A type II variation was approved to remove the contraindication against concomitant use of verapamil and aliskiren from the Summary of Product Characteristics of Rasilez and RasilezHCT (II/41 and II/05-G, approved in March 2011) and to include a statement with regard to potential for interaction with organic anionic transporting polypeptide (OATP) inhibitors and with rifampicin. Corresponding amendments were also introduced into the Patient leaflet. The present variation application is submitted to introduce the same changes to the Product Information for all aliskiren-containing medicinal products. The proposed changes to the product information are acceptable.</p> |

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|           | particular to new quality, pre-clinical, clinical or pharmacovigilance data  |  |   |   |         |
| IG/0088/G | This was an application for a group of variations.<br>C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD, C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system | 11/07/2011   | n/a   |   |         |
| WS/0139/G | This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br>To add a new manufacturing site, Novartis Grimsby Ltd, UK, for the intermediates of aliskiren, respectively C3 and C6.<br>Together with this change, several changes have been introduced to the reagents, solvents, starting material specifications and batch size at the proposed site.<br><br>B.I.a.1.a - Change in the manufacturer      | 23/06/2011   | 23/06/2011  |   |         |

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|         | <p>of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer,</p> <p>B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the currently approved batch size,</p> <p>B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits,</p> <p>B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method,</p> <p>B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter),</p> <p>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation,</p> <p>B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure</p> |  |   |   |  |
| WS/0098 | This was an application for a variation  | 14/04/2011   | 18/05/2011  | SPC, PL   | Following the review of PSUR 5 for aliskiren MAH was |

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|         | <p>following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.8 of the SmPC to add the Adverse Drug Reaction 'hypersensitivity reactions' under post-marketing experience as requested by CHMP following PSUR review. The Package Leaflet has been updated accordingly. In addition, the MAH takes the opportunity to update the contact details in the Package Leaflet of the local representative in Poland. This application was submitted for a group of variations consisting of Type II variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data</p> |  |   |   | <p>requested to consider updating the SmPC to add severe cutaneous adverse reactions (SCARs) and arthralgia. Conducted review of all cases of SCARs and of arthralgia did not demonstrate an evidence of a clear causal relationship between these events and aliskiren treatment. However, the analysis revealed a possible relationship between these events and hypersensitivity. Subsequently MAH has performed a detailed analysis of available data. The evidence presented is considered to support the inclusion of post-marketing events of "hypersensitivity" into the SmPC section 4.8 (undesirable effects) for aliskiren.</p> |
| WS/0055 | <p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.2 and 5.1 of the SmPC to include information about the efficacy and safety of aliskiren in elderly and very elderly hypertensive patients based on data from the AGELESS study.</p>   | 14/04/2011   | 18/05/2011  | SPC   | <p>AGELESS study was conducted in order to specifically evaluate the safety and efficacy of aliskiren and aliskiren/HCT in elderly (&gt;65ys) and very elderly (&gt;75 ys) hypertensive patients. Overall the results of this clinical study support the conclusion of a positive benefit/risk ratio in the use of the aliskiren+HCTZ as antihypertensive treatment of elderly and very elderly patients. However, the review of available data also suggests different response to the treatment of elderly and very elderly. As a result sections 4.2 and 5.1 have</p>   |



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|         | C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data   |  |   |   | been updated by including information about the efficacy and safety of aliskiren in elderly and very elderly hypertensive patients.   |
| WS/0073 | <p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. This type II variation concerns an update of sections 4.2 and 4.5 of the SPC in view of the results of study CSPP100A2112 investigating the potential interaction between aliskiren and grapefruit juice in healthy subjects. The Package Leaflet has been updated accordingly.</p> <p>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data</p> | 17/02/2011   | 24/03/2011  | SPC   | <p>This type II variation concerns an update of section 4.5 of the SPC in view of the results of study CSPP100A2112 investigating the potential interaction between aliskiren and grapefruit juice in healthy subjects. Administration of grapefruit juice with aliskiren resulted in a decrease in AUC and Cmax of aliskiren. Co-administration with aliskiren 150 mg resulted in a 61% decrease in aliskiren AUC and co-administration with aliskiren 300 mg resulted in a 38% decrease in aliskiren AUC. This decrease is likely due to an inhibition of organic anion transporting polypeptide-mediated uptake of aliskiren by grapefruit juice in the gastrointestinal tract. Therefore, because of the risk of therapeutic failure, grapefruit juice should not be taken together with aliskiren.</p> <p>This application was submitted for a Type II variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> |
| WS/0028 | <p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of Summary of Product Characteristics and Package Leaflet.</p> <p>C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP,</p>   | 20/01/2011   | 22/02/2011  | SPC, PL   | <p>This type IB variation concerns an update of section 4.8 of the SPC, upon request by CHMP following the assessment of PSURs 4 and 5 for aliskiren, to add the ADR 'blood creatinine increase' under post-marketing experience. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to make some minor editorial changes to the safety information already included in section 4.8 of the SPC. This application was submitted as a Type IB variation following a worksharing procedure according to Article 20</p>  |

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|           | FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH   |  |   |   | of Commission Regulation (EC) No 1234/2008. |
| IB/0041/G | <p>This was an application for a group of variations.</p> <p>B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms,</p> <p>B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms,</p> <p>B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms,</p> <p>B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms,</p> <p>B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms,</p> <p>B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms,</p> <p>B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms,</p> <p>B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms,</p> <p>B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms,</p> | 28/01/2011   | 28/01/2011  | SPC, Labelling, PL                              |   |



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|    | <p>B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms,</p> <p>B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms,</p> <p>B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms,</p> <p>B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms,</p> <p>B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms,</p> <p>B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms,</p> <p>B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms,</p> <p>B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms</p> |  |   |   |         |

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| IB/0042/G | <p>This was an application for a group of variations.</p> <p>A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS,</p> <p>A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS,</p> <p>B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation</p> | 27/01/2011   | n/a   |   |  |
| WS/0069   | <p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>This type IB variation concerns an update of sections 4.3, 4.4 and 4.8 of the SPC, upon request by CHMP following a review by the PhVWP of the risk of angioedema with aliskiren, to add the new contraindication 'hereditary or idiopathic angioedema' and to add further information about the risk of angioedema with aliskiren administration.</p>  | 16/12/2010   | 21/01/2011  | SPC   | <p>This type IB variation concerned an update of sections 4.3, 4.4 and 4.8 of the SPC, upon request by CHMP following a review by the PhVWP of the risk of angioedema with aliskiren, to add the new contraindication 'hereditary or idiopathic angioedema' and to add further information about the risk of angioedema with aliskiren administration.</p> <p>The application was submitted for a Type IB variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>See scientific discussion EMA/H/C/XXXX/WS/0069.</p> |

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|           | C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH   |  |   |   |   |
| IG/0032/G | <p>This was an application for a group of variations.<br/>Update of Summary of Product Characteristics, Labelling and Package Leaflet<br/>To implement Core Data Sheet changes in the relevant sections of the EU SmPC. The proposed changes in the SmPC are also reflected in the corresponding sections of the labelling and PL. As part of the outcome of assessment of FUM 007, 5.2 of SmPC is updated to include data from paediatric study DAP-PEDS- 07-02. The "Annex II B. Conditions for the marketing authorisation" has been updated to include the key messages of the additional risk minimisation activities described in the EU Risk Management Plan, already in place in Member States.</p> <p>C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the OPFV,</p> | 21/12/2010   | n/a   | Annex II  | <p>This was an application for a group of variations. Core Data Sheet changes in the relevant sections of the EU SmPC are implemented. The proposed changes in the SmPC are also reflected in the corresponding sections of the labelling and PL. As part of the outcome of assessment of FUM 007, 5.2 of SmPC is updated to include data from paediatric study DAP-PEDS- 07-02. The "Annex II B. Conditions for the marketing authorisation" has been updated to include the key messages of the Additional Risk Minimisation Activities described in the EU Risk Management Plan, already in place in Member States.</p> <p>Core Data Sheet changes: Changes are made to SmPC, labelling and PL, in order to be consistent with relevant changes made to the Novartis Cubicin Basic Prescribing Information.</p> <p>DAP-PEDS- 07-02: A study was conducted to evaluate the pharmacokinetics of daptomycin after a single 8 mg/kg or 10 mg/kg dose of Cubicin as either a 1 or 2 hour infusion in paediatric subjects aged 2 to 6 years, inclusive, with proven or suspected Gram-positive infections who were receiving standard antibiotic therapy. The mean exposure (AUC<sub>0-8</sub>) was approximately 429 and 550 µg*hr/ml after the administration of 8 and 10 mg/kg single doses, respectively, similar to the exposure seen in adults at the 4 mg/kg dose at steady state (495 µg*hr/ml). The</p> |

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|---------|--|--|---|---|---|
|         | C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD, C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system |  |   |   | pharmacokinetics of daptomycin appears to be linear in the dose range studied. The half life, clearance and volume of distribution were similar at both dose levels. Risk minimisation Activities: The additional risk minimisation activities mentioned in the Risk Management Plan in the form of dosage card and laboratory susceptibility testing leaflet were in place for Cubicin because of concerns over medication errors, severe skeletal muscle toxicity and interference with coagulation tests results. It was recognised that these measures are very important for the safe and effective use of the product, hence, the CHMP recommended that this was made a condition of the Marketing Authorisation.   |
| WS/0037 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of Summary of Product Characteristics, Annex II and Package Leaflet<br><br>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data  | 23/09/2010   | 25/10/2010  | SPC, Annex II, PL                               | This type II variation concerned an update of section 4.3 of the SPC to add a contraindication for the concomitant use of aliskiren and itraconazole, and section 4.5 of the SPC to add information regarding this interaction following the publication of a study in healthy subjects. The Package Leaflet has been updated accordingly. A study in healthy volunteers showed that itraconazole (100 mg) increases AUC and C <sub>max</sub> of aliskiren (150 mg) by 6.5-fold and 5.8-fold, respectively. Therefore, concomitant use of aliskiren and the potent P-gp inhibitor itraconazole is contraindicated. In addition, the MAH took the opportunity to update the annexes in line with the latest QRD template (version 7.3). This application was submitted for a Type II variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. |
| WS/0056 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Increase of the batch size for the   | 21/10/2010   | 21/10/2010  |   |   |

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|---------|---|--|---|---|---|
|         | intermediate B3<br><br>B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the currently approved batch size  |  |   |   |   |
| WS/0027 | <p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. This type IB variation concerns an update of section 4.8 of the SPC, upon request by CHMP following the assessment of PSUR 3 and PSUR 4, to include information about the ADR 'peripheral oedema'. The Package Leaflet has been updated accordingly.</p> <p>C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH</p> | 23/09/2010   | 15/10/2010  | SPC, PL   | <p>This variation concerns an update of section 4.8 of the SPC, upon request by CHMP following the assessment of PSUR 3 and PSUR 4, to include information about the ADR 'peripheral oedema'. The Package Leaflet has been updated accordingly.</p> <p>The application was submitted for a Type IB variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Peripheral oedema has been reported with aliskiren use in the post-marketing setting. The detailed analysis of spontaneous reports showed that many cases were confounded by patient medical history or suspect concomitant medication. Nevertheless, a number of cases showed a positive de-challenge such that a causal relationship to treatment could not be excluded. Therefore, based on this analysis, and in accordance with CHMP's requests following assessment of PSUR 3 and PSUR 4 for aliskiren, the MAH applied for a variation to update the 'Undesirable effects' section of the SPC to add the text: "Post marketing experience: peripheral oedema (frequency unknown)". The Package Leaflet has also been updated accordingly.</p> |
| WS/0030 | <p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>B.I.a.3.a - Change in batch size</p>  | 23/09/2010   | 23/09/2010  |   |   |



| No      | Scope   | Opinion/<br>Notification <sup>1</sup><br>issued on | Commission<br>Decision<br>Issued <sup>2</sup> /<br>amended on | Product<br>Information<br>affected <sup>3</sup> | Summary  |
|---------|---|--|---|---|--|
|         | (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the currently approved batch size  |  |   |   |  |
| IG/0011 | B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method | 01/07/2010   | n/a   |   |  |
| II/0039 | Update of the Detailed Description of the Pharmacovigilance system (DDPS).<br><br>Update of DDPS (Pharmacovigilance)  | 18/02/2010   | 23/03/2010  | Annex II  | With this variation the MAH submitted a new version of the DDPS (core version 8.0 and product specific version 6.0) in accordance with the current Pharmacovigilance guideline. After assessing the documentation the CHMP concluded that the submitted DDPS contained all required elements.  |
| IB/0038 | 33_Minor change in the manufacture of the finished product  | 29/04/2009   | n/a   |   |  |
| IB/0036 | 07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release   | 29/04/2009   | n/a   |   |  |
| II/0034 | Update of SPC section 5.1 to delete the existing sentence relating to elevated plasma renin activity and cardiovascular outcomes.<br><br>Update of Summary of Product Characteristics                                 | 19/03/2009   | 22/04/2009  | SPC   | The following sentence has been deleted from SPC section 5.1 based on the fact that currently no data are available to directly link the reduction in renin activity induced by aliskiren with effects on cardiovascular outcomes: "Elevated PRA has been independently associated with increased cardiovascular risk in hypertensive and normotensive patients." as currently there is no evidence available proving that changes in renin activity induced by antihypertensive drugs might have an important role in cardiovascular disease. |

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|---------|---|--|---|---|---|
| II/0033 | <p>Update of SPC section 4.4 to include a warning of events of renal dysfunction in at-risk patients and to amend the existing text for renal artery stenosis following the CHMP assessment of PSURs. SPC section 4.8 has been updated relating to events of renal dysfunction and acute renal failure during post-marketing experience. The package leaflet has been amended accordingly.</p> <p>Update of Summary of Product Characteristics and Package Leaflet</p>  | 19/02/2009   | 03/04/2009  | SPC, PL   | <p>For aliskiren, cases of renal dysfunction with relevant occurrence were reported in the postmarketing use (PSUR 1 and PSUR 2).</p> <p>Following evaluation of the available postmarketing data, the CHMP concluded to add a warning to SPC section 4.4 that caution should be exercised when aliskiren is given in the presence of conditions pre-disposing to kidney dysfunction such as hypovolemia (eg. due to blood loss, severe or prolonged diarrhea, prolonged vomiting, etc.), heart disease, liver disease or kidney disease. Acute renal failure, reversible upon discontinuation of treatment, has been reported in at-risk patients receiving aliskiren in post-marketing experience.. In the event that any signs of renal failure occur, aliskiren should be promptly discontinued. Furthermore, SPC section 4.8 was also amended.</p> |
| II/0031 | <p>Update of SPC sections 4.3 and 4.4 to include a contraindication on the use in patients with prior history of angioedema and a warning of angioedema-type reactions as for other agents acting on the renin-angiotensin system respectively, following the CHMP assessment of PSURs. Furthermore, SPC section 4.8 has been revised regarding angioedema cases and the Package Leaflet has been updated in accordance with the SPC changes.</p> <p>Update of Summary of Product Characteristics and Package Leaflet</p> | 19/02/2009   | 03/04/2009  | SPC, PL   | <p>For aliskiren, cases of angioedema with relevant occurrence were reported in the postmarketing use. Following the assessment of the available data, the CHMP concluded that a contraindication for patients with a history of angioedema with aliskiren is needed. In addition, a warning of angioedema-type reactions as for other agents acting on the renin-angiotensin system has been added to SPC section 4.4 recommending that patients without a previous history who suffer angioedema with aliskiren should discontinue treatment and contact their doctor. Furthermore, the term "angioedema" has been added as a rare adverse drug reaction to SPC section 4.8.</p>  |
| II/0032 | <p>Update of SPC section 4.5 to include a statement regarding the potential interaction with non-steroidal anti-</p>  | 19/02/2009   | 03/04/2009  | SPC, PL   | <p>The MAH was requested to add a statement regarding the potential for interaction between NSAID's and agents acting on the Renin Angiotensin System to SPC section</p>  |

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|         | inflammatory agents (NSAIDs). The package leaflet has been amended accordingly.<br><br>Update of Summary of Product Characteristics and Package Leaflet   |  |   |   | 4.5. As with other agents acting on the renin - angiotensin system, NSAIDs may reduce the anti-hypertensive effect of aliskiren. In some patients with compromised renal function (dehydrated patients or elderly patients) aliskiren given concomitantly with NSAIDs may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore the combination of aliskiren with an NSAID requires caution, especially in elderly patients. The package leaflet has been amended accordingly.  |
| IA/0035 | 07_a_Replacement/add. of manufacturing site: Secondary packaging site,<br>07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms  | 11/02/2009   | n/a   |   |   |
| IA/0037 | 32_a_Change in batch size of the finished product - up to 10-fold   | 11/02/2009   | n/a   |   |   |
| II/0029 | Update of or change(s) to the pharmaceutical documentation  | 23/10/2008   | 04/11/2008  |   |   |
| II/0026 | Update of SPC section 4.3 "Contraindications" and section 4.5 "Interactions" following new information from a cyclosporine drug-drug interaction study (SPP100A2106) which was subject to a Follow-Up Measure. Further revisions were introduced to section SPC sections 4.4 "Warnings and Precautions for use" and 4.5. The package leaflet has been amended accordingly. In addition, minor corrections have been included in the relevant sections of SPC, | 24/07/2008   | 28/08/2008  | SPC, Labelling, PL                              | The results of the cyclosporine interaction study in 14 subjects showed that concomitant cyclosporine administration increased AUC 4.5 to 5.5 fold with a lower dose of aliskiren (75 mg) than the authorised strengths (150 and 300mg). Also cyclosporine markedly increased aliskiren t1/2. Hence, there is concern that the increase in AUC would be substantially higher with the approved aliskiren dosage, even exceeding the highest dose tested in humans. An additional concern is that aliskiren might distribute to tissues from which the medicinal product is normally absent in presence of a P-gp inhibitor, or preset at low levels because of the activity of P-gp. Non clinical and clinical data converge to show that P-gp is a major |

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|---------|---|--|---|---|---|
|         | <p>labelling and package leaflet with regard to the active substance (aliskiren hemifumarate) and also for PL section 5.</p> <p>Update of Summary of Product Characteristics, Labelling and Package Leaflet</p> |  |   |   | <p>determinant of aliskiren bioavailability. In addition, literature data show that P-gp mediates tissue uptake of a variety of P-gp substrates and that P-gp inhibitors can markedly increase the tissue-to-plasma concentration ratios.</p> <p>Given the very limited safety data at increased exposure, and the risk for very large increase in tissue exposure, the CHMP concluded that the co-administration of cyclosporine and aliskiren poses serious safety concerns. Therefore, a contraindication for the concomitant administration with cyclosporine, a highly potent P-gp inhibitor, as well as with other potent P g inhibitors (verapamil, quinidine) is considered essential. Moreover, due to the risk for higher increase in tissue exposure than in plasma, caution should be advised during co administration with moderate P-gp inhibitors (ketoconazol, itraconazol, clarithromycin, telithromycin, erythromycin, amiodarone).</p> |
| II/0030 | Update of or change(s) to the pharmaceutical documentation  | 24/07/2003   | 29/07/2008  |   |   |
| II/0027 | <p>Update of the SPC section 4.4 and 5.1 following new information from a study (SPP100A2313) in patients with heart failure.</p> <p>Update of Summary of Product Characteristics</p>                           | 30/05/2003   | 09/07/2008  | SPC   | <p>Study SPP100A2313, a 12-week double-blind, randomised, placebo-controlled, 2-arm study of aliskiren 150 mg od added to standard therapy in patients with stable heart failure evaluated the overall safety and tolerability of aliskiren 150 mg when given in addition to standard therapy in hypertensive patients with stable heart failure. The study included 302 patients with mild to moderate heart failure.</p> <p>Addition of 150 mg aliskiren showed a reduction of BNP levels by 25 %, although the clinical significance of this reduction is unknown. No statistically significant differences in signs and symptoms of heart failure were found and overall grading of patients according to NYHA classification remained unchanged.</p>   |

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| II/0028 | Update of SPC section 5.1<br>"Pharmacodynamic Properties" with<br>efficacy data from a clinical study<br>(study SPP100C2201) in patients with<br>nephropathy.<br><br>Update of Summary of Product<br>Characteristics | 30/05/2008   | 09/07/2008  | SPC   | Study SPP100C2201, a 6 monthly randomised, double-blind, placebo-controlled study investigated the effects of aliskiren (150mg / 300mg) on proteinuria in 599 patients with hypertension and Type II 2 diabetes mellitus in whom blood pressure had been previously controlled by means of an angiotensin receptor blocker (losartan) in combination with the optional use of other antihypertensive drugs (hydrochlorothiazide and/or amlodipine). The addition of 300mg aliskiren achieved an average reduction in the urinary albumin to creatinine (UACR) ratio of 12 mg/mmol (from 58 to 46 mg/mmol) compared to placebo. Aliskiren did not induce any significant effect on blood pressure or affect estimated GFR under these conditions. The clinical relevance of a reduction in UACR is not established in the absence of an effect on blood pressure. Furthermore, aliskiren was associated with an increased frequency (4.2% vs. 1.9% for placebo) in serum potassium concentration (? 6 mmol/l). |
| IB/0012 | 10_Minor change in the manufacturing<br>process of the active substance,<br>12_b_02_Change in spec. of active<br>subst./agent in manuf. of active subst.<br>- test parameter   | 31/01/2008   | n/a   |   |   |
| IB/0002 | 12_b_02_Change in spec. of active<br>subst./agent in manuf. of active subst.<br>- test parameter   | 13/11/2007   | n/a   |   |   |
| IB/0001 | 12_b_02_Change in spec. of active<br>subst./agent in manuf. of active subst.<br>- test parameter   | 13/11/2007   | n/a   |   |   |
| IA/0014 | 11_a_Change in batch size of active<br>substance or intermediate - up to 10-<br>fold   | 12/11/2007   | n/a   |   |   |
| IA/0019 | 11_a_Change in batch size of active  | 12/11/2007   | n/a   |   |   |

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|---------|---|--|---|---|---------|
|         | substance or intermediate - up to 10-fold                                     |  |   |   |         |
| IA/0015 | 11_a_Change in batch size of active substance or intermediate - up to 10-fold | 12/11/2007   | n/a   |   |         |
| IA/0020 | 11_a_Change in batch size of active substance or intermediate - up to 10-fold | 12/11/2007   | n/a   |   |         |
| IA/0016 | 11_a_Change in batch size of active substance or intermediate - up to 10-fold | 12/11/2007   | n/a   |   |         |
| IA/0017 | 11_a_Change in batch size of active substance or intermediate - up to 10-fold | 12/11/2007   | n/a   |   |         |
| IA/0018 | 11_a_Change in batch size of active substance or intermediate - up to 10-fold | 12/11/2007   | n/a   |   |         |
| IA/0013 | 11_a_Change in batch size of active substance or intermediate - up to 10-fold | 12/11/2007   | n/a   |   |         |